RTS,S/AS01 Candidate Malaria vaccine
Summary for the SAGE meeting

October 2009
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1. BACKGROUND

1.1. Burden of *Plasmodium falciparum*

In 2007, there were more than 2.37 billion people living in areas where *Plasmodium falciparum* malaria transmission occurs [Guerra, 2008]. Sub-Saharan Africa carries the highest burden of the disease with an estimated 250 million cases and nearly one million deaths each year [WHO, 2008b; Greenwood, 2008]. Over 80% of these deaths occur among African children under the age of five years [UNICEF and RBM, 2007]. Malaria represents a huge burden on health care systems as it accounts for 30-50% of all outpatient care and 50% of pediatric hospital admissions [UNICEF and RBM, 2007].

Currently implemented malaria control strategies include interventions such as insecticide-treated nets (ITN); intermittent preventive treatment to pregnant women (IPTp); and Artemisinin based combination treatment (ACT). In addition, intermittent preventive treatment to infants (IPTi) and children (IPTc) has been evaluated in pilot countries and is under assessment for possible implementation in some endemic settings. Countries that have successfully implemented large scale malaria control programs, such as Rwanda, Zambia, Madagascar, have already demonstrated a decrease of the malaria burden [WHO, 2008a]. Implementation and scaling-up of the currently available malaria control strategies should continue.

While epidemiology of malaria in Africa is changing, history has shown that a range of tools are needed, and that over-reliance on any one intervention may not provide a long-term solution. It is critical to fully implement existing tools to prevent and treat malaria. It is also critical to build the next generation of tools, to complement those of today, in order to address malaria over the decades to come. The broad implementation of a safe and effective malaria vaccine will be one such critical tool [WHO&UNICEF, 2005]. The Malaria Vaccine Technology Roadmap has defined in 2006, as a target for the first generation malaria vaccine, a vaccine providing 50% efficacy against severe malaria disease and death, lasting for more than 1 year [www.MalariaVaccineRoadmap.net].

The development of RTS,S/AS malaria vaccine is being conducted by GSK in collaboration and partnership: the early stage development was undertaken in collaboration with WRAIR (Walter Reed Army Institute of Research, US) and the paediatric clinical development through an innovative Public Private Partnership with PATH-Malaria Vaccine Initiative (MVI), funded by the Bill & Melinda Gates Foundation (BMGF). Clinical trials are carried out with African Research Institutes and their Northern hemisphere partners.

Modeling suggests that “vaccines with efficacy similar to that of RTS,S/AS” have the potential to reduce malaria morbidity and mortality during the first decade after their introduction [Maire, 2006]. Vaccine introduction decisions will need to be made in the context of scaling-up of ITN, ACT and other control measures. We therefore plan to provide information to enable assessment of RTS,S/AS performance in the context of various site-specific malaria control implementation settings. Combination of RTS,S/AS
vaccine with other malaria control measures should maximize impact on malaria morbidity and mortality in infants and young children in Africa.

1.2. The RTS,S/AS01 vaccine candidate: product formulation, presentation & packaging

The approach of GlaxoSmithKline (GSK) Biologicals in designing the RTS,S/AS01 vaccine against *P. falciparum* has been to target the free sporozoite and intra-hepatic stages of the parasites (i.e. the pre-erythrocytic stage). The hypothesized mode of action of such vaccine is to induce circulating antibodies that reduce the load of sporozoites reaching the liver, and in addition to stimulate T-cell responses that promote the destruction of infected liver cells and impede further intracellular parasite development. This would lead to a significant decrease in infection rates in vaccinees and in the load of parasites emerging from the liver with a subsequent impact on disease rate and severity.

The active substance in our candidate malaria vaccine is a recombinant antigen expressed in *Saccharomyces cerevisiae* coded RTS,S. The RTS,S antigen consists of two proteins, RTS and S, that spontaneously assemble into mixed polymeric particulate structures intracellularly:

- RTS is a hybrid polypeptide consisting of a portion of the circumsporozoite protein (CS), a sporozoite surface antigen of the malaria parasite *P. falciparum* strain NF54, fused to the amino-terminal end of the hepatitis B virus S protein.
- S designates the surface antigen of Hepatitis B virus and is the same antigen used in GSK Biological's licensed Hepatitis-B vaccines.

GSK Proprietary AS01 Adjuvant System consists of a liquid suspension of liposomes with two immunostimulant components: 3’-O-desacyl-4’-monophosphoryl lipid A (MPL) and *Quillaja saponaria* 21 (QS21). There are no AS01 adjuvanted vaccines licensed yet, although MPL is a component of some licensed vaccines such as the GSK human papillomavirus (HPV) vaccine.

The RTS,S antigen and the Adjuvant System are stable in the refrigerator (2-8°C): available stability data support 3 years shelf-life for both. The final vaccine for administration is obtained by reconstituting a lyophilized preparation of RTS,S antigen with AS01 and has to be injected intra-muscularly, within 6 hours of reconstitution, in accordance with current WHO policies for lyophilised vaccines.

For future use in immunization programs, the vaccine presentation and packaging shall align with WHO/UNICEF procurement specifications including application of a vaccine vial monitor.
2. CLINICAL DEVELOPMENT OF RTS,S/AS VACCINE CANDIDATE

2.1. Overview of pediatric phase II data in children and infants

This section briefly summarises results from Phase II trials conducted with the various formulations of adjuvanted RTS,S/AS vaccine. In early studies, RTS,S antigen was adjuvanted with AS02 Adjuvant System which contains the same immunostimulants, MPL and QS21, in the same amount as the current AS01 Adjuvant System but uses a proprietary oil-in-water emulsion as vehicle in lieu of liposomal suspension.

Efficacy:

Vaccine efficacy (VE) of the earlier formulation RTS,S/AS02 against malaria disease, including severe malaria disease, has been demonstrated in a large trial that enrolled 2,022 children aged 1 to 4 years from an area of high malaria transmission (Mozambique). Over the first 18 months of follow-up, the efficacy against first clinical malaria episode (defined as \( P. falciparum \) parasitemia > 2500/µl and fever \( \geq 37.5^\circ C \)) was 35.3% (95%CI: 21.6, 46.6) and against severe malaria disease was 48.6% (95%CI: 12.3, 71.0) [Alonso, 2005]. Clinical benefit persisted for 3.5 years after vaccination (VE against clinical malaria of 30.5% over 42 months), with no rebound of malaria cases in the RTS,S/AS02 vaccinated group [Sacarlal, 2009].

A recent clinical study has been conducted with the final formulation RTS,S/AS01 to assess clinical malaria efficacy. In this trial in Kenya and Tanzania, vaccine efficacy against malaria disease observed in children 5 to 17 months of age vaccinated with 3 doses of the RTS,S/AS01 was 52.9% (95% CI: 28.1, 69.1; mean follow-up time of 8 months) [Bejon, 2008]. Long-term follow-up data are pending from this promising study.

In addition, proof of concept of vaccine efficacy against \( P. falciparum \) infection (65.9%; 95%CI: 42.6, 79.8) and against clinical malaria disease (65.8%; 95%CI: 25.3, 84.4) has been demonstrated with RTS,S/AS02 in infants from 6 weeks of age followed during 3 months [Aponte, 2007]. A similar efficacy against infection (65.2%; 95%CI: 20.7, 84.7) was shown after 6 months of follow-up when RTS,S/AS02 was co-administered with DTPw/Hib and OPV vaccines according to the EPI schedule [Abdulla, 2008].

Safety

Both formulations of RTS,S/AS vaccine have been shown to have an acceptable clinical safety profile when administered to infants and children in sub-Saharan Africa. In total, more than 8,000 doses of RTS,S/AS have been administered to over 3,000 infants and children.

In two large controlled studies that enrolled 890 and 2,022 subjects, less serious adverse events (SAEs) were reported by subjects vaccinated with RTS,S/AS as compared with subjects that received control vaccines (this difference was statistically significant in the larger trial [Sacarlal, 2009]). Similarly, there was a trend in reduction of all cause mortality and hospital admissions in the long-term follow-up of the study in children 1 to
4 years old [Sacarlal, 2009]. The reactogenicity (solicited local and general symptoms) of the RTS,S/AS vaccine was comparable to that induced by DTPw combination vaccines [Abdulla, 2008; Aponte, 2007].

At end of phase II studies, a pooled analysis of all pediatric safety data was conducted. In general, injection-induced local inflammatory signs and systemic symptoms occurring during the 7 days and 30 days following vaccination were similar between study and comparator vaccines. A lower SAE rate was observed in the RTS,S/AS group that was only partly accounted for by a reduction in the number of malaria SAEs. A reduction in lower respiratory tract infection was also seen, suggesting that preventing malaria through vaccination may have indirect as well as direct effects. Some trials have suggested indirect effects of the use of insecticide-treated nets [Binka, 2002], but this has not been confirmed in other studies [Nevill, 1996]. The possible indirect benefits of vaccination will be examined further in a phase III trials.

In the pooled analysis, there was an imbalance observed for non-serious rashes, which will be further monitored in Phase III trials. This pooled analysis and overall safety data were presented to WHO Global Advisory Committee for Vaccine Safety (GACVS) in June 2009. The GACVS concluded that, based on the data available from phase I/II studies, the RTS,S/AS01 had an acceptable safety profile [WHO, 2009]. We understand that GACVS will review the Phase III safety database once available.

**Immunogenicity**

Adjuvanted RTS,S/AS02 and RTS,S/AS01 vaccines induced high anti-CS antibody titres as compared to control groups. The RTS,S/AS01 formulation induced higher anti-CS peak antibody titres than the RTS,S/AS02 formulation. A higher peak response was reached when RTS,S/AS02 was given according to the 0, 1, 2-month schedule as compared to the 0, 1, 7-month schedule. A high and persistent antibody response against hepatitis B antigen was observed in all clinical studies.

When RTS,S/AS02 was co-administered with DTPw/Hib at 8, 12 and 16 weeks of age, seroprotection/serositivity levels for D, T, Pw and Hib antigens were high (> 95%) in all groups and the pre-defined non-inferiority criteria for these antigens were met [Abdulla, 2008]. A phase II trial with RTS,S/AS01 given in co-administration with routine EPI vaccines (DTPwHepB/Hib, OPV, measles and yellow fever) in infants from 6 weeks of age, is ongoing.

**Conclusion**

The RTS,S/AS candidate malaria vaccine adjuvanted with GSK’s proprietary Adjuvant System has consistently demonstrated efficacy in clinical trials conducted in pediatric populations in malaria endemic countries. This efficacy has been shown to extend from infection to the most severe forms of the disease with clinical benefit persisting over 3.5 years. The efficacy against severe malaria and trends in deaths reduction seen in Phase II studies give an indication of the possibility of substantial reductions in mortality after RTS,S/AS immunization, to be further evaluated in the Phase III trial. In addition, the RTS,S/AS candidate malaria vaccine had an acceptable clinical safety profile when given to young children and infants in co-administration with routine EPI vaccines.
These clinical results were presented in June 2009 to the WHO Initiative for Vaccine Research (IVR) / Global Malaria Programme (GMP) Joint Technical Expert Group (JTEG).

2.2. Selection of the vaccine dose, Adjuvant System and schedule

The 25 µg antigen dose has been selected based on safety and immunogenicity studies in children 1 to 11 years old [Bojang, 2005]. Indeed, while the association between high anti-CS antibody titres and protection against clinical malaria is not demonstrated, there is an association between higher antibody titres and protection against infection. From these trials, the 25 µg antigen dose was selected due to equivalent anti-CS antibody response and slightly less reactogenicity compared to the 50 µg antigen dose group. Immunogenicity was low with the 10 µg antigen vaccine.

The RTS,S/AS01 Adjuvant System has been selected for progression into phase III for the following reasons:

- Extensive non-clinical studies demonstrated the need for specific adjuvantation to optimize RTS,S antigen immunogenicity. This was observed for both humoral and CMI responses. Among all tested Adjuvant Systems, the ones including both MPL and QS21 immunostimulants proved to be the most effective immunologically [Garçon, 2003].

- Both RTS,S/AS01 and RTS,S/AS02 formulations of the vaccine have shown efficacy against infection in human challenge model trials in USA and against clinical malaria disease in field trials. However the RTS,S/AS01 formulation has shown a trend for better efficacy in the challenge model [Kester, 2009]. In children 5 to 17 months of age living in endemic areas, vaccine efficacy against clinical disease of 53% (95% CI: 28, 69) was demonstrated with RTS,S/AS01 [Bejon, 2008].

- RTS,S/AS01 formulation has shown an acceptable safety profile. Reactogenicity is comparable to that induced by routine DTPw combination vaccines and incidence of local reactions tended to be lower than with the RTS,S/AS02 formulation [Kester, 2009; Lell, 2009, submitted; Owusu Agyei, 2009, submitted].

- RTS,S/AS01 has been shown to induce a stronger anti-CS antibody response than RTS,S/AS02 in children [Lell, 2009, submitted, Owusu Agyei, 2009, submitted].

- Preclinical and clinical comparative studies confirmed the superiority of AS01 in terms of humoral and cell-mediated immune (CMI) responses when combined with a variety of malarial and non-malarial antigens [Mettens, 2008; Stewart 2006; Kester, 2009]. A growing clinical database of AS01-adjuvanted vaccines (malarial and non-malarial antigens) provides also further assurance about the safety of this adjuvant in humans [WHO 2009].

The 0, 1, 2-month schedule has been selected for progression into phase III for the following reasons:

- A third dose of RTS,S/AS01 or RTS,S/AS02 resulted in a marked increase in anti-CS and anti-HBs titres, as compared to two doses at 0, 1 month, indicating an added

- The 0, 1, 2-month schedule is compatible with the EPI immunization schedule. The results from the phase II clinical trials support the administration of the RTS,S vaccine according to the 0, 1, 2-month schedule, starting at 6 weeks of age in co-administration with 3 doses of DTPw combination vaccine or starting at 5 to 17 months of age [Abdulla, 2008; Bejon, 2008].

- VE against *P. falciparum* infection, against clinical and severe malaria disease was demonstrated at various ages with RTS,S/AS vaccine given according to this 0, 1, 2-month schedule.

- This schedule provides more rapid protection than the 0, 1, 7-month schedule and should encourage better compliance for the 3rd dose.

2.3. **Overview of the Phase III clinical development plan**

The pivotal phase III study is a multi-center efficacy trial aiming to confirm VE against clinical malaria disease and provide data of VE against more severe forms of the disease. It is further described in section 2.4.

The population of the multi-center efficacy trial will mirror as closely as possible the population of children who usually attend EPI visits. Low birth weight infants, malnourished children and potentially HIV infected children will be eligible. For safety reasons, those that are critically sick will be excluded, in particular any child that requires hospital admission or is at an advanced stage of HIV disease (WHO classification grade 3 or 4). A dedicated study is planned in children seropositive for HIV. This trial will enrol 200 HIV infected infants and children and will be a controlled, randomised, double blind study with safety follow-up up to one year after the last RTS,S vaccine dose as primary objective and immunogenicity as secondary objective.

We have planned for the possibility that pneumoccocal conjugated vaccine and rotavirus vaccine will be implemented as EPI vaccines in sub-saharan Africa in the near future. Safety and immunogenicity of RTS,S/AS01 in co-administration with rotavirus and *S. pneumoniae* conjugated vaccines will therefore be evaluated in a separate study within the phase III program. Non-inferiority of the immune response to rotavirus and pneumoccocal antigens, when co-administered with RTS,S/AS01 vaccine, as compared to these antigens co-administered with a licensed hepatitis B vaccine will be evaluated. The same study should support also an indication of prevention of hepatitis B for RTS,S/AS01.

Another trial in the phase III program aims to demonstrate lot-to-lot consistency and will evaluate immunogenicity and safety of 3 lots of RTS,S/AS01 vaccine.

The research teams at each study centre will ensure that malaria control measures, including insecticide treated bednets, are used in accordance with National policies,
2.4. The pivotal phase III efficacy study

2.4.1. Study design

The study was designed in consultation with the malaria scientific community, WHO [Moorthy 2007, Moorthy 2009], FDA, EMEA and African National Regulatory Authorities. The study protocol was approved by African NRAs following a joint review process organised by WHO, and by the relevant local and national Ethical Review Boards (study protocol posted on ClinicalTrials.gov, identifier NCT00866619). It is a multi-centre, observer blind, participant blind, randomised controlled study in children aged 6 weeks to 17 months at the time of first vaccination, from diverse malaria transmission settings across Africa. The proposed primary immunisation schedule is a 3-dose regimen with a one month interval between sequential doses, i.e. a 0, 1, 2-month schedule. In the infants 6 to 12 weeks of age, the RTS,S/AS01 vaccine will be given in co-administration with the 3 doses of the primary course of DTPw-HepB/Hib and OPV vaccines. Children randomized to the control group will receive 3 doses of a cell-culture rabies vaccine if they are 5-17 months of age or 3 doses of a Meningoccocal C vaccine (in co-administration with DTPw-HepB/Hib and OPV vaccines) if they are 6-12 weeks of age.

The duration of efficacy and the impact of a booster dose of RTS,S/AS01 will be evaluated by comparing groups receiving RTS,S/AS01 in primary vaccination and a booster dose of RTS,S/AS01 or control vaccine at 18 months after completion of the primary immunization (≥ 20 months from first dose) (see Figure 1 for study design). Control vaccines are Meningococcal C or rabies vaccines in the 5-17 months group and Meningococcal C vaccines in the 6-12 weeks group (see table below). All infants in the 6-12 weeks group will receive concomitantly an OPV booster dose.

A maximum of 16,000 children in two age categories will be included in the trial:

- a minimum of 6,000 children ≥ 5 months to 17 months of age who will be randomised (1:1:1 ratio) to receive:
  
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<th>Primary on a 0, 1, 2-month schedule</th>
<th>Boost 20 months after first dose</th>
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<tr>
<td>Group 1</td>
<td>RTS,S/AS01</td>
<td>RTS,S/AS01</td>
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<td>Group 2</td>
<td>RTS,S/AS01</td>
<td>Meningococcal C vaccine</td>
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<td>Group 3</td>
<td>Rabies vaccine</td>
<td>Rabies vaccine</td>
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- a minimum of 6,000 children from 6 to 12 weeks of age who have not received a DTPw containing vaccine will be randomised (1:1:1 ratio) to receive:

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<th>Primary on a 0, 1, 2-month schedule*</th>
<th>Boost 20 months after first dose</th>
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<tbody>
<tr>
<td>Group 1</td>
<td>RTS,S/AS01 + DTPwHepB/Hib + OPV</td>
<td>RTS,S/AS01 + OPV</td>
</tr>
<tr>
<td>Group 2</td>
<td>RTS,S/AS01 + DTPwHepB/Hib + OPV</td>
<td>Meningococcal C vaccine + OPV</td>
</tr>
<tr>
<td>Group 3</td>
<td>Meningococcal C vaccine + DTPwHepB/Hib + OPV</td>
<td>Meningococcal C vaccine + OPV</td>
</tr>
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* in co-administration with DTP1, DTP2 and DTP3 doses at 6, 10, 14 weeks of age.
Malaria case definitions have been set in agreement with WHO recommendations [Moorthy 2007]. Case assessment is according to a protocol-specified algorithm and training on assessment of clinical signs has been given to all physicians. Determination of *Plasmodium falciparum* asexual parasite density will be determined according to standardised methods across all centres. The parasite density will be determined independently by two readers and in the case of non-concordance, a third read will be carried out. Accuracy of results will be assured through an external Quality Assessment Program according to WHO recommendation [WHO, 2006] to accredit each reader every 3 months.

With respect to the use of malaria control measures, Intermittent Preventative Treatment for malaria in infants (IPTi) and indoor residual spraying will be recorded throughout the study. Bednet use will be determined at two home visits during the study (at month 14 and at month 32). The 2 timepoints selected correspond to timepoints for efficacy analysis, for which bednet use is a variable to adjust vaccine efficacy. The sponsor believes that direct observation of bednet use just before database closure for efficacy analysis provides a more reliable measure than recording usage at study start. Indeed, as 10 out of the 11 centres will distribute bednets at screening, it is likely that a majority of the parents would report their intend to use it.

In addition, per recommendation from JTEG, GSK/MVI are currently planning to conduct surveys for parasite prevalence in children < 5 years at community level to evaluate malaria transmission at study sites.

*P. falciparum* strain selection has not been observed in Phase II studies [Alloueche 2005, Enosse 2007]. Additional data will be collected in this phase III study.

2.4.2. **Objectives of the study**

Co-primary objectives are the efficacy against clinical malaria disease after primary immunisation in each of the two age categories. All participating centres will use
standardised case definitions for efficacy endpoints and a structured approach to case-assessment. Cases of clinical disease will be pooled across participating centres to determine the primary endpoint of efficacy against clinical disease in each age category.

Secondary objectives will assess the efficacy of the vaccine on severe malaria disease, severe anaemia and malaria hospitalization on the pooled age groups. Analysis by site will allow the evaluation of efficacy under different conditions of malaria transmission and randomisation to a booster dose will allow the evaluation of the duration of efficacy of a primary course and the requirement for boosting.

Other objectives include determination of efficacy of the vaccine against non-malaria serious morbidity, malaria-specific mortality and all-cause mortality. In addition, correlation between anti-CS serology and protection will be investigated.

Analyses planned during the trial:

- Primary analysis to investigate efficacy against clinical malaria disease after completion of primary immunization series by at least 6,000 children 5-17 months at first dose (4,000 RTS,S/AS01 recipients). This analysis will be triggered when all children have completed 12 months follow-up after last vaccination dose, or when 450 subjects experience a case, whichever occurs later. If 450 malaria cases are not accumulated by the time of boost at 18 months follow-up, the analysis will proceed.

- Primary analysis to investigate efficacy against clinical malaria disease after completion of primary immunization series by at least 6000 infants 6 to 12 weeks at first dose (4,000 RTS,S/AS01 recipients). This analysis will be triggered when all infants have completed 12 months follow-up, or when 450 subjects experience a case, whichever occurs later. If 450 malaria cases are not accumulated by the time of boost the analysis will proceed.

- A secondary analysis for evaluation of efficacy against severe disease. This analysis will proceed when 250 cases of severe malaria are accumulated in both age groups.

- A final analysis will be carried out at the end of the trial after 30 months of follow-up after the third dose for all subjects and will include further investigations of vaccine efficacy against a range of manifestations of malaria disease, such as severe malaria disease, severe anemia, hospitalization due to malaria, etc and will evaluate immunogenicity of a RTS,S/AS01 booster dose.

It should be noted that the co-primary analyses pertain to different endpoints in different age groups and therefore no data is analysed twice.

2.4.3. Duration of follow-up

The total duration of the phase III efficacy study is 32 months for all subjects. Half of the RTS,S/AS01 vaccinees (minimum 4,000) will receive a RTS,S/AS01 booster dose 18 months after the last dose of the primary vaccination schedule and will be followed for a further 12 months. The other half of the RTS,S/AS01 vaccinees (minimum 4,000) will not receive a RTS,S/AS01 booster and therefore will be followed during 30 months after primary vaccination schedule.
2.4.4. Status of enrollment

The pivotal phase III efficacy study is currently ongoing in 9 out of the 11 sites in Tanzania, Mozambique, Kenya, Gabon, Malawi and Ghana. The enrollment has started with the children from 5 to 17 months. Infants’ enrollment should start as of October 2009.

3. HEALTH ECONOMIC ANALYSIS PLANS

Adopting a new intervention into African health systems requires extensive policy processes, supported by multifaceted data. Decision-makers in countries and international organizations will require robust evidence to make an informed decision about introduction of a new strategy. The role of RTS,S/AS01 vaccine will need to be considered in combination with existing control strategies such as ITNs, indoor spraying (IRS) and anti-malaria drugs and to be understood in the context of other new EPI vaccines. Health economic analyses will need to determine the cost-effectiveness of RTS,S/AS01, as well as help countries understand the impact on national health budgets.

Estimating the cost-effectiveness and budget impact will require a mixture of primary data collection in Africa and modelling, confirmed with results from ongoing studies and planned phase III trials.

GSK and MVI anticipate conducting a series of health economic and budget impact analyses over the coming years in further consultation with external advisory bodies and the WHO Quantitative Immunization and Vaccines Related Research (QUIVER) Technical Advisory Committee.

4. NEXT STEPS TOWARDS IMPLEMENTATION

The RTS,S/AS01 candidate malaria vaccine will be manufactured in Europe, and is intended for malaria endemic countries of Sub-Saharan Africa where the medical need is the highest. Therefore, GSK Biologicals will be seeking a scientific evaluation of the vaccine by the European Medicines Agency (EMEA) using the provision of Article 58 of the current European Council (EC) regulation of medicinal products (EC No 726/2004), whereby the EMEA may give a Scientific Opinion, in cooperation with WHO, for the evaluation of certain medicinal products for human use intended exclusively for markets outside the European Union.

Marketing authorisation application should be submitted to African National Regulatory Authorities, on the basis of Article 58 positive opinion. Finally, WHO Prequalification will be sought in a timely fashion to support the use of the vaccine in routine vaccination programs supported by United Nations Agencies such as UNICEF.

GSK Biologicals is currently discussing with EMEA the regulatory submission strategy, with the aim to making the vaccine available as soon as possible to children in malaria endemic countries of Sub-Saharan Africa.

The MVI-GSK partnership will also consult experts and WHO on post-approval activities. A JTEG review on this topic will be organised in 2010.
5. REFERENCES


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